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Cross-Metathesis

Olefin-Bond Chemodifferentiation through Cross-Metathesis Reactions: A Stereocontrolled Approach to Functionalized $\beta^{2,3}$-Amino Acid Derivatives

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Abstract: Substituted cyclopentanes or tetrahydrofurans bearing two vinyl groups have been investigated in cross-metathesis reactions to explore chemodiscrimination of the two olefin bonds. The syntheses consisted of ring opening of constrained unsaturated β-lactams or bicyclic β-amino acids, followed by cross-metathesis to test the chemodifferentiation of the divinyl-substituted azetidinones or β-amino esters in the presence of various ruthenium-based catalysts.

Introduction

In the last two decades, olefin metathesis reactions have revolutionized organic synthesis. This has been made possible by the development and commercial availability of catalysts with high activities and remarkable functional-group tolerance.[1] Using this process, many natural products and biologically active compounds have been synthesized that were previously unavailable or hard to prepare by any other means.[2]

Olefin metathesis can be carried out in a chemoselective manner in several ways. The outcome of the reaction is often catalyst-dependent.[3] Steric or electronic deactivation of one of the C–C double bonds can also induce chemoselectivity.[4] Furthermore, several studies reported plausible hydrogen-bonding interactions in the preassembly phase between the chloride ligand of the catalyst and a hydrogen atom of the substrate; this would then favour the selective transformation of a particular C–C double bond.[5]

Although they are less abundant than their α-analogues, conformationally constrained β-amino acids have received enormous attention in the last 20 years as a consequence of their high biological relevance. These compounds not only occur in nature either as small molecular entities or as part of more complex molecules, but also function as precursors of β-lactams. Moreover, certain carbocyclic β-amino acids such as the five-membered carbocyclic cispentacin (isolated from the culture broth of a *Bacillus cereus*) or icofungipen have antifungal activities.[6] Since the new-generation peptides constructed from β-amino acids are stable to metabolism, proteases, and peptidases, they are regarded as important biomolecules for medicinal chemistry.[7] Furthermore, β-lactams have attracted widespread attention over the last 70 years because of their high antibiotic activity. Despite the spread of resistance, compounds with a 2-azetidinone framework are still among the most commonly used antibiotics.[8] In addition to their antibiotic properties, the β-lactam framework has been extensively used as a versatile synthon to access a wide variety of organic molecules.[9]

Results and Discussion

In this paper, we present our findings on the olefin-bond chemodifferentiation in cross-metathesis reactions (CM) of some divinylated β-amino acid derivatives and divinylated β-lactams, which leads to the formation of monocoupled products in a chemoselective manner.

Recently, we reported the synthesis of new difunctionalized azetidin-2-ones and β-amino acid derivatives through stereocontrolled ring-opening metathesis (ROM) reactions with ethylene, induced by available Ru-based catalysts. After the ROM reaction, the newly formed olefin bonds were further functionalized through CM reactions with α,β-unsaturated ketones or α,β-unsaturated esters.[10] During our recent experimental investigation, we realized that under appropriately chosen reaction conditions, chemodiscrimination of the olefinic bonds in CM reactions is achievable. For this reason, we selected diolefinated cyclic derivatives fused with a β-lactam skeleton or cyclic frameworks containing two different functional groups. The model compounds are esters and protected amino (β-amino acid) derivatives. The aim of this study was to construct monocoupled β-lactams and cyclic β-amino acid derivatives, and to investigate the chemical behaviour of the C=C bonds involved in these transformations.

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We started our experiments by investigating the CM reaction of divinyl-substituted azetidinone (±)-**2**, derived from lactam (±)-**1**.[10b] Lactam (±)-**2** was subjected to a CM reaction with methyl vinyl ketone or acrylic esters in the presence of commercially available Grubbs 1st generation, Grubbs 2nd generation, Hoveyda–Grubbs 1st generation, and Hoveyda–Grubbs 2nd generation catalysts. Cross-metathesis products were detected only in the presence of the Hoveyda–Grubbs 2nd generation catalyst (HG-2).

Through varying the amount of catalyst (e.g., 1 or 2 mol-%), temperature (room temperature or reflux), and reaction time (e.g., 2, 4, or 12 h), we found that the best selectivity was obtained by using 5 mol-% HG-2 catalyst in dry CH_2Cl_2 for 4 h. Under these conditions, monometathesized products (±)-**3** or (±)-**4** were isolated in moderate yields. In the products, the α,β-unsaturated carbonyl or ester moiety is located near to the amide nitrogen atom (Scheme 1). Unfortunately, our attempts to increase the yields of the monocoupled products by variation of the experimental conditions failed as a result of various side reactions (polymerization, formation of dicoupled products).

We assume that stereochemical factors (chelate-ring stability), hydrogen-bonding ability, and the distance between the NH group and the C=C bond might be responsible for the observed selectivity in the CM reaction. All of these factors may affect the outcome of the reaction to some extent. In particular, although it is less known in metal-catalysed processes,[5] we suppose that a hydrogen-bonding interaction between the chlorine atom of the catalyst and the amide N–H moiety as a hydrogen-bond donor group could direct the olefin bond closer to the amide nitrogen atom to participate in the coupling reaction (Figure 1). This leads to the monocoupled product before further coupling can occur.

Monocoupled β-lactams (±)-**3a** and (±)-**3b** are valuable precursors for the synthesis of functionalized cispentacins through opening of the lactam ring. Thus, monocoupled cispentacin hydrochlorides (±)-**5a** and (±)-**5b** were synthesized from the corresponding β-lactams (±)-**3a** and (±)-**3b** by ethanolysis [in the case of (±)-**3a**, transesterification did not occur]. Next, the

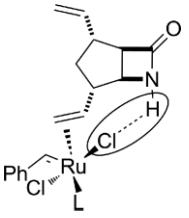
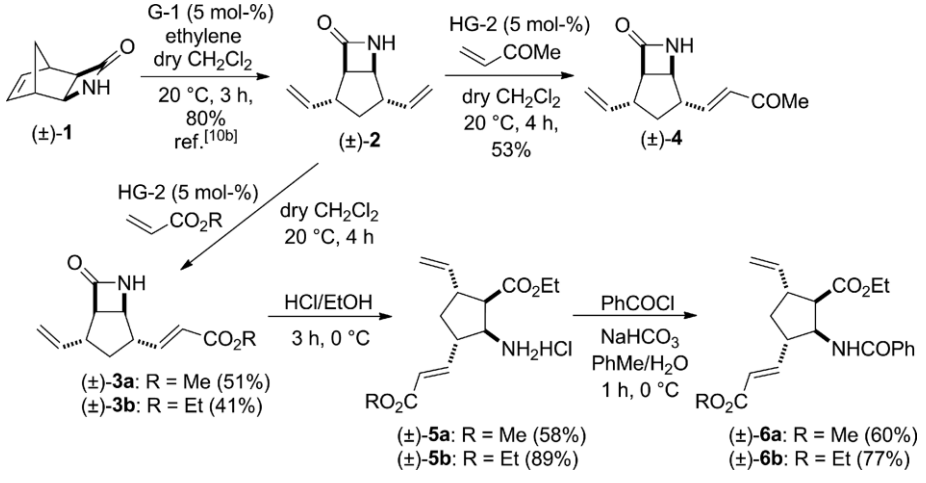


Figure 1. Hydrogen-bonding interaction between the chlorine atom of the catalyst and the amide N–H moiety.

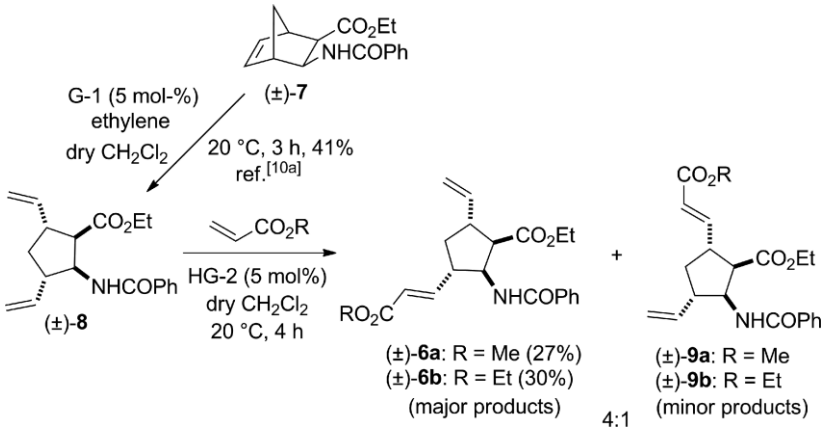
products were subjected to benzoylation to give new monocoupled β-amino acid derivatives (±)-**6a** and (±)-**6b** (Scheme 1).

Expanding our investigation of olefin-bond chemodifferentiation through cross-metathesis, cyclic β-amino acids containing a five-membered ring were next used as model starting compounds. Divinyl-substituted cispentacin (±)-**8**, prepared by our recently published ROM method,[10a] was submitted to the CM reaction. In contrast to lactam (±)-**2**, the cross-metathesis reaction of compound (±)-**8** with the α,β-unsaturated carbonyl compound and esters to give monocoupled products was not 100 % selective. As determined by ^{1}H NMR spectroscopic analysis, a mixture of the two regioisomers (±)-**6** and (±)-**9** was formed in a 4:1 ratio as a result of a partial hydrogen-bonding directing effect (Scheme 2). The major product (±)-**6** was isolated by crystallization from hexane/EtOAc, and its NMR spectroscopic data were identical with those of the final product presented in Scheme 1. Unfortunately, the minor product (±)-**9** could not be isolated in pure form either by crystallization or chromatography. Further experiments with variation of the catalyst quantity or using portionwise addition did not give better results: the dicoupled derivative and/or a polymeric material was formed.

We were interested in investigating the hydrogen-bonding directing effect by carrying out experiments using a starting material that cannot function as a hydrogen-bond donor. To test our hypothesis, *N*-Boc-protected (Boc = *tert*-butoxycarbonyl) β-lactam (±)-**10**,[11] which cannot act as a hydrogen-bond donor, was subjected to CM with ethyl acrylate in the presence of the HG-2 catalyst.

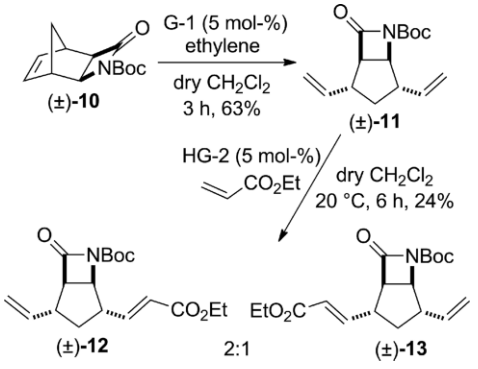


Scheme 1.



Scheme 2.

In this case, as expected, when the directing effect was excluded, the coupling reaction led to a mixture of the two monometathesized isomers (±)-**12** and (±)-**13** in nearly 2:1 ratio, as determined by NMR spectroscopic analysis of the crude mixture (Scheme 3). Our efforts to separate and isolate these two isomers failed. Nevertheless, the NMR spectra clearly indicated that (±)-**12** and (±)-**13** were the only products present in the mixture.

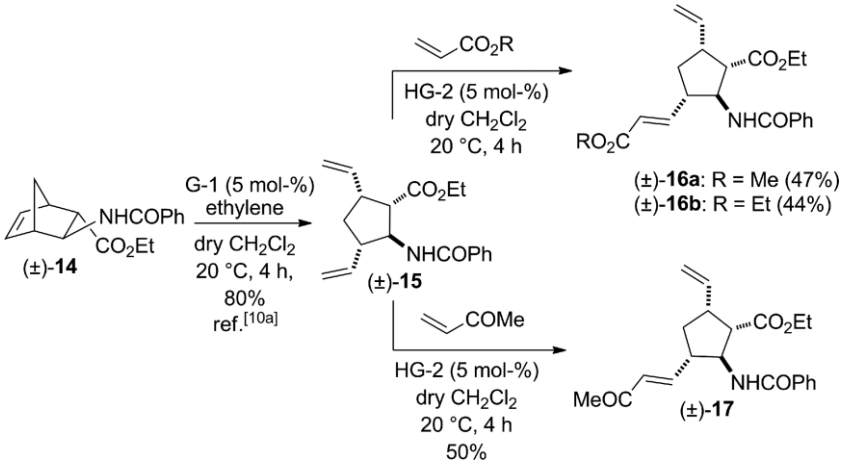


Scheme 3.

The synthetic route developed for the preparation of monocoupled β-amino acid derivatives could be extended to the synthesis of divinylated transpentacins.

For this purpose, diolefinated amino ester (±)-**15** [derived from (±)-**14** by ROM],[10a] where the protected amino group and the ester group are in a *trans* relationship, was subjected to cross-metathesis carried out at room temperature in dry CH_2Cl_2 with methyl vinyl ketone and acrylic esters in the presence of the HG-2 catalyst. In contrast with divinyl-cispentacin (±)-**8**, the single monocoupled isomers (±)-**16a**, (±)-**16b**, and (±)-**17** were formed (Scheme 4). The structure of (±)-**16a** was also confirmed by X-ray crystallography (Figure 2).

Since hydrogen-bond-acceptor solvents can disrupt the hydrogen-bonding interaction between the catalyst and the substrate, we planned to investigate the effect of solvents on the CM reaction. The reaction of compound (±)-**15** with methyl acrylate (which in CH_2Cl_2 selectively gave a single regioisomer) was carried out in three additional solvents. The results show that solvents that can participate in hydrogen bonding with the substrate (dioxane, THF), compete with the catalyst, resulting in the formation of a mixture of products (±)-**16a** and (±)-**18** (approximately 2:1 ratio, as detected by NMR spectroscopic



Scheme 4.

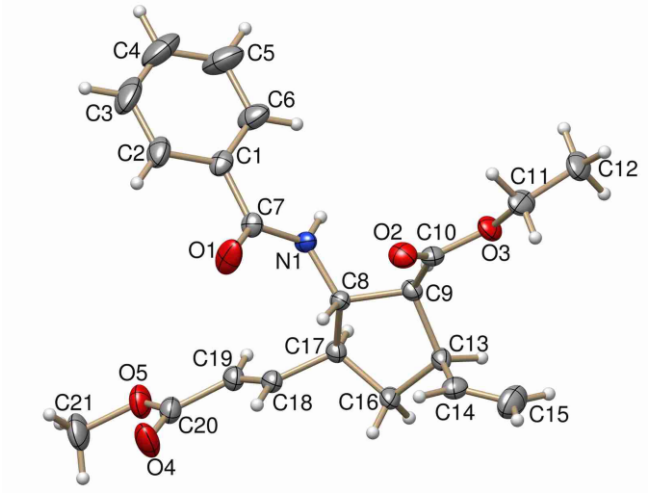


Figure 2. X-ray structure of compound (±)-**16a**.

analysis of the crude reaction mixture). In contrast, solvents that cannot form a hydrogen bond (CH_2Cl_2, PhMe) clearly gave only a single regioisomer (Schemes 4 and 5).

Interestingly, when another transpentacin stereoisomer, namely (±)-**20** [derived from amino ester (±)-**19**],[10a] was subjected to the CM reaction with either methyl vinyl ketone or acrylic esters, an inseparable mixture of regioisomers (±)-**21**/(±)-**22** or (±)-**23**/(±)-**24**, respectively, was formed, each in a nearly 2:1 ratio (Scheme 6).

These results suggest that in addition to the hydrogen-bonding effect, another factor also influences the outcome of the coupling reactions. The chemoselectivity may originate from steric effects. It is also highly probable that coordination of the ruthenium atom to the carbonyl oxygen atom, which creates a stable six-membered chelate ring, stabilizes the metallacyclobutane and hinders further transformations. For **T2** and **T3**, structures in which the vinyl side-chain and the ester group are *trans* to each other, formation of the chelate ring is less favourable, and so the cross-metathesis reaction is not selective (Figure 3).

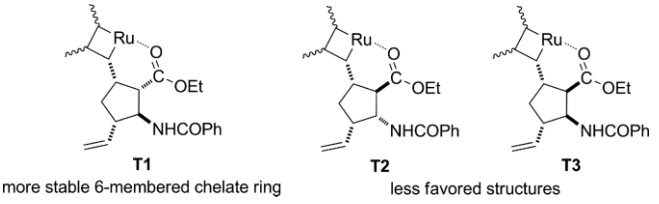
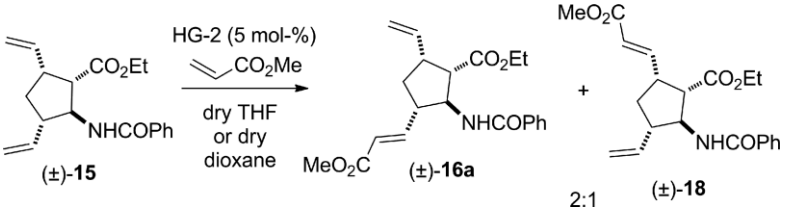
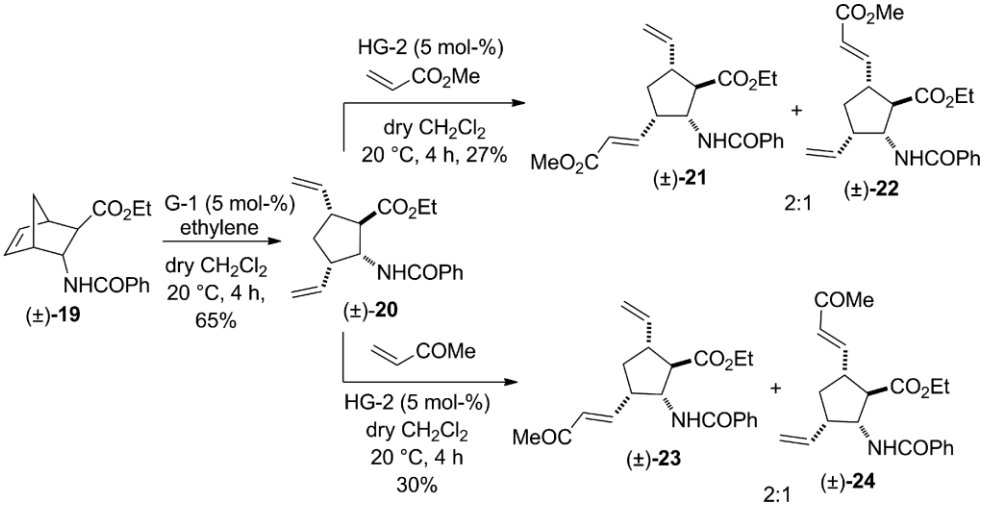


Figure 3. Structures of metallacyclobutane intermediates.

Since oxygen-containing heterocyclic β-amino acids (e.g., oxetin)[6a] play an important role in medicinal chemistry, we extended the CM-based chemoselective functionalization approach to the preparation of substituted oxygen heterocycles. Thus, divinylated amino ester (±)-**26** [derived from (±)-**25** through ROM],[10a] in which the ester and amide groups have a *cis* relationship, was treated with ethyl acrylate to give an

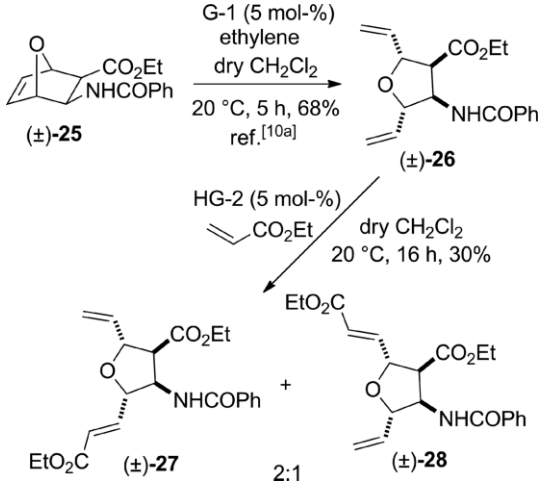


Scheme 5.



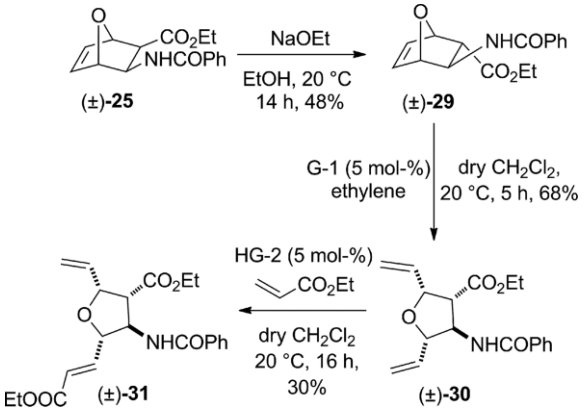
Scheme 6.

inseparable mixture of the two regioisomers (±)-**27** and (±)-**28** in a nearly 2:1 ratio (Scheme 7).



Scheme 7.

Next, it seemed logical to evaluate the behaviour of compound (±)-**30**, the *trans* counterpart of (±)-**26**. For this reason, compound (±)-**29**, obtained by isomerization of (±)-**25** through its active hydrogen atom, was transformed by ROM into divinylated derivative (±)-**30**.[10a] Reaction of the latter with ethyl acrylate in the presence of HG-2 led, analogously to divinylated *trans* amino ester (±)-**15**, to monocoupled derivative (±)-**31** as the sole product (Scheme 8).



Scheme 8.

Conclusions

Transformations involving the chemodifferentiation of various divinylated functionalized cyclopentanes and bicyclic azetidinones were investigated under cross-metathesis reaction conditions. Depending on their structure, the CM reaction of diolefinated β-amino acids or β-lactams selectively gave valuable functionalized olefinated derivatives. A hydrogen-bonding directing effect and stereochemical factors involving chelate-ring formation proved to be responsible for the chemodiscrimination; these factors were also supported by NH–NBoc exchange and solvent effects. The functionalized products synthesized might be interesting scaffolds for peptides or for medicinal chemistry, and may serve as interesting building blocks in organic synthesis.

Experimental Section

General Procedure for the Cross-Metathesis: β-Lactam (±)-**2**, (±)-**11** or β-amino ester (±)-**8**, (±)-**15**, (±)-**20**, (±)-**26**, (±)-**30** (100 mg) was dissolved in anhydrous solvent (20 mL), and catalyst (5 mol-%; see Schemes) and methyl vinyl ketone, methyl acrylate, or ethyl acrylate (5 equiv.) were added. The mixture was stirred for the time and temperature indicated. When TLC indicated that the reaction was complete, the mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

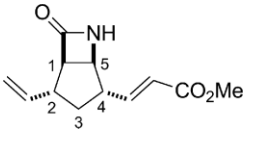
General Procedure for the Ring-Opening Metathesis: β-Lactam (±)-**1**, (±)-**10** (100 mg) or β-amino ester (±)-**7**, (±)-**14**, (±)-**19**, (±)-**25** (100 mg) was dissolved in anhydrous CH_2Cl_2 (20 mL), and catalyst (5 mol-%) was added. The mixture was stirred at 20 °C under ethylene for the time indicated (monitored by TLC). When the reaction was complete, the mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

General Procedure for the Preparation of Amino Ester Hydrochlorides: β-Lactam (±)-**3a** or (±)-**3b** (100 mg) was dissolved in EtOH (2 mL), and HCl solution (30 % in EtOH; 5 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 5 min, then it was warmed to room temperature; stirring was continued for 3 h. When TLC indicated that the reaction was complete, the mixture was concentrated under reduced pressure, and the residue was purified by washing with Et_2O.

General Procedure for the Preparation of *N*-Benzoyl-Protected Amino Esters: Amino ester hydrochloride (±)-**5a** or (±)-**5b** (1.4 mmol) was dissolved in toluene (30 mL). A solution of $NaHCO_3$ (1.1 g) in H_2O (20 mL) was added at 0 °C, followed by the dropwise addition of benzoyl chloride (1 equiv.). The reaction mixture was stirred at 0 °C for 1 h, then it was diluted with EtOAc (70 mL), and the mixture was washed with H_2O (3 × 50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was crystallized from *n*-hexane/Et_2O to give the *N*-benzoylamino ester.

General Procedure for the Isomerization Reaction: NaOEt (1.5 equiv.) was added to a solution of *cis*-*N*-protected amino ester (±)-**25** (3.5 mmol) in EtOH (30 mL) at 0 °C, and the mixture was stirred at 20 °C for 14 h. Then H_2O (70 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was dried with Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 4:1) to give the *trans* isomer.

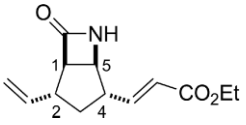
Methyl (*E*)-3-[(1*R,2*R**,4*S**,5*S**)-7-Oxo-2-vinyl-6-azabicyclo-[3.2.0]heptan-4-yl]acrylate [(±)-3a]**



Brown oil (69 mg, 51 %). R_f = 0.44 (*n*-hexane/EtOAc, 1:3). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.94 (d, J = 14.0 Hz, 1 H, 3-H), 2.48–2.59 (m, 1 H, 3-H), 2.89 (t, J = 8.0 Hz, 1 H, 4-H), 3.02–3.12 (m, 1 H, 2-H), 3.64 (s, 1 H, 1-H), 3.73 (s, 3 H, OCH_3), 4.06 (d, J = 4.0 Hz, 1 H, 5-H), 4.97–5.12 (m, 2 H, =CH), 5.67–5.89 (m, 2 H, =CH), 6.32 (br. s, 1 H, NH),

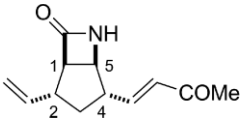
6.78–6.94 (m, 1 H, =CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.1, 41.3, 45.0, 52.1, 59.2, 61.6, 115.2, 121.9, 141, 149.8, 167.0, 170.2 ppm. MS (ESI): *m/z* = 222.25 $[M + H]^+$. $C_{12}H_{15}NO_3$ (221.26): calcd. C 65.14, H 6.83, N 6.33; found C 64.85, H 6.66, N 6.52.

Ethyl (*E*)-3-[(1*R,2*R**,4*S**,5*S**)-7-Oxo-2-vinyl-6-azabicyclo[3.2.0]-heptan-4-yl]acrylate [(±)-3b]**



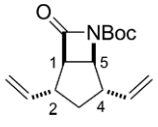
Brown oil (59 mg, 41 %). R_f = 0.46 (*n*-hexane/EtOAc, 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 8.0 Hz, 3 H, CH_3), 1.94 (d, *J* = 8.0 Hz, 1 H, 3-H), 2.45–2.60 (m, 1 H, 3-H), 2.83–2.94 (m, 1 H, 4-H), 3.02–3.11 (m, 1 H, 2-H), 3.63 (s, 1 H, 1-H), 4.03–4.10 (m, 1 H, 5-H), 4.12–4.24 (m, 2 H, OCH_2), 4.95–5.13 (m, 2 H, =CH), 5.65–5.89 (m, 2 H, =CH), 6.29 (br. s, 1 H, NH), 6.78–6.94 (m, 1 H, =CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 37.0, 41.4, 45.2, 59.2, 60.8, 61.7, 115.1, 122.3, 140.9, 149.3, 166.6, 170.1 ppm. MS (ESI): *m/z* = 236.34 $[M + H]^+$. $C_{13}H_{17}NO_3$ (235.28): calcd. C 66.36, H 7.28, N 5.95; found C 66.13, H 7.02, N 5.77.

(1*R,2*R**,4*S**,5*S**)-4-[(*E*)-3-Oxobut-1-en-1-yl]-2-vinyl-6-azabicyclo[3.2.0]heptan-7-one [(±)-4]**



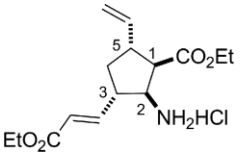
Brown oil (67 mg, 53 %). R_f = 0.61 (*n*-hexane/acetone, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95 (d, *J* = 16.0 Hz, 1 H, 3-H), 2.21 (s, 3 H, CH_3), 2.49–2.60 (m, 1 H, 3-H), 2.91 (t, *J* = 8.00 Hz, 1 H, 4-H), 3.03–3.11 (m, 1 H, 2-H), 3.67 (s, 1 H, 1-H), 4.07 (d, *J* = 4.00 Hz, 1 H, 5-H), 5.00–5.11 (m, 2 H, =CH), 5.70–5.83 (m, 1 H, =CH), 6.02–6.11 (m, 1 H, =CH), 6.54 (br. s, 1 H, NH), 6.64–6.74 (m, 1 H, =CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.3, 37.1, 41.1, 45.1, 59.2, 61.3, 115.0, 131.5, 141.3, 148.7, 170.2, 198.6 ppm. MS (ESI): *m/z* = 206.11 $[M + H]^+$. $C_{12}H_{15}NO_2$ (205.26): calcd. C 70.22, H 7.37, N 6.82; found C 70.03, H 7.14, N 6.63.

***tert*-Butyl (1*R**,2*R**,4*S**,5*S**)-7-Oxo-2,4-divinyl-6-azabicyclo[3.2.0]heptane-6-carboxylate [(±)-11]**



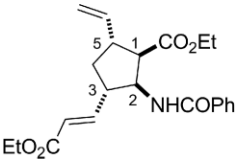
Brown oil (71 mg, 63 %). R_f = 0.64 (*n*-hexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (s, 9 H, CH_3), 1.83–1.93 (m, 1 H, 3-H), 2.29–2.41 (m, 1 H, 3-H), 2.96–3.11 (m, 2 H, 4-H, 2-H), 3.48–3.52 (m, 1 H, 1-H), 4.25 (d, *J* = 4.8 Hz, 1 H, 5-H), 4.96–5.17 (m, 4 H, =CH), 5.73–5.87 (m, 2 H, =CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5, 37.7, 42.3, 45.0, 59.9, 63.3, 115.0, 116.2, 139.6, 141.1, 167.3, 168.5 ppm. MS (ESI): *m/z* = 286.00 $[M + Na]^+$. $C_{15}H_{21}NO_3$ (263.34): calcd. C 68.42, H 8.04, N 5.32; found C 68.18, H 7.84, N 5.10.

Ethyl (1*R,2*S**,3*S**,5*R**)-2-Amino-3-[(*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]-5-vinylcyclopentanecarboxylate Hydrochloride [(±)-5b]**



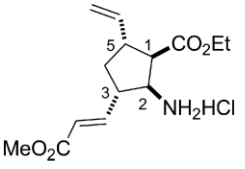
White solid (120 mg, 89 %). M.p. 121–124 °C. R_f = 0.67 (CH_2Cl_2/MeOH, 95:5). ^{1}H NMR (400 MHz, $[D_6]$DMSO): δ = 1.12–1.26 (m, 6 H, CH_3), 1.40–1.55 (m, 1 H, 4-H), 2.04–2.17 (m, 1 H, 4-H), 2.87–3.05 (m, 3 H, 1-H, 3-H, 5-H), 3.60–3.72 (m, 1 H, 2-H), 4.02–4.21 (m, 4 H, OCH_2), 4.92–5.13 (m, 2 H, =CH), 5.72–6.02 (m, 2 H, =CH), 6.86–7.00 (m, 1 H, =CH), 8.26 (br. s. 3 H, NH) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO): δ = 14.9, 15.1, 36.7, 46.7, 46.9, 51.2, 56.0, 60.8, 61.7, 116.5, 123.2, 139.9, 148.6, 166.5, 171.8 ppm. MS (ESI): *m/z* = 282.21 $[M + H]^+$. $C_{15}H_{24}ClNO_4$ (317.81): calcd. C 56.69, H 7.61, N 4.41; found C 56.49, H 7.44, N 4.14.

Ethyl (1*R,2*S**,3*S**,5*R**)-2-Benzamido-3-[(*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]-5-vinylcyclopentanecarboxylate [(±)-6b]**



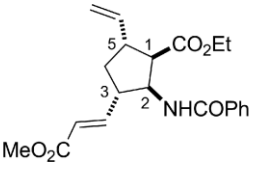
White solid (93 mg, 77 %). M.p. 107–110 °C. R_f = 0.52 (*n*-hexane/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 8.0 Hz, 3 H, CH_3), 1.27 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.45–1.58 (m, 1 H, 4-H), 2.13–2.24 (m, 1 H, 4-H), 2.86–2.97 (m, 1 H, 3-H), 2.98–3.10 (m, 2 H, 1-H, 5-H), 4.00–4.23 (m, 4 H, OCH_2), 4.61–4.73 (m, 1 H, 2-H), 5.00–5.15 (m 2 H, =CH), 5.75–5.96 (m, 2 H, =CH), 6.83 (d, *J* = 8.0 Hz, 1 H, NH), 6.88–6.98 (m, 1 H, =CH), 7.37–7.46 (m, 2 H, Ar-H), 7.46–7.53 (m, 1 H, Ar-H), 7.69–7.76 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 14.6, 36.8, 47.0, 49.2, 52.2, 55.7, 60.8, 61.5, 115.8, 122.9, 127.3, 129.0, 132.1, 139.7, 148.1, 166.5, 167.2, 174.5 ppm. MS (ESI): *m/z* = 386.25 $[M + H]^+$. $C_{22}H_{27}NO_5$ (385.46): calcd. C 68.55, H 7.06, N 3.63; found C 68.22, H 6.88, N 3.12.

Ethyl (1*R,2*S**,3*S**,5*R**)-2-Amino-3-[(*E*)-3-methoxy-3-oxoprop-1-en-1-yl]-5-vinylcyclopentanecarboxylate Hydrochloride [(±)-5a]**



White solid (80 mg, 58 %). M.p. 116–118 °C. R_f = 0.64 (CH_2Cl_2/MeOH, 95:5). ^{1}H NMR (400 MHz, $[D_6]$DMSO): δ = 1.20 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.41–1.54 (m, 1 H, 4-H), 2.05–2.16 (m, 1 H, 4-H), 2.90–3.01 (m, 3 H, 1-H, 3-H, 5-H), 3.64–3.69 (m, 4 H, OCH_3, 2-H), 4.05–4.20 (m, 2 H, OCH_2), 4.99–5.11 (m, 2 H, =CH), 5.73–5.85 (m, 1 H, =CH), 5.98 (d, *J* = 12.0 Hz, 1 H, =CH), 6.88–6.98 (m, 1 H, =CH), 8.21 (br s. 3 H, NH) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO): δ = 15.0, 36.6, 46.7, 46.9, 51.2, 52.3, 56.0, 61.7, 116.6, 122.9, 140.0, 148.8, 168.3, 171.9 ppm. MS (ESI): *m/z* = 268.18 $[M + H]^+$. $C_{14}H_{22}ClNO_4$ (303.79): calcd. C 55.35, H 7.30, N 4.61; found C 55.16, H 7.12, N 4.42.

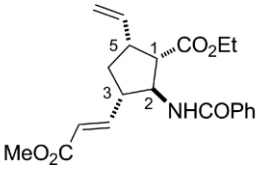
Ethyl (1*R,2*S**,3*S**,5*R**)-2-Benzamido-3-[(*E*)-3-methoxy-3-oxoprop-1-en-1-yl]-5-vinylcyclopentanecarboxylate [(±)-6a]**



White solid (73 mg, 60 %). M.p. 137–141 °C. R_f = 0.49 (*n*-hexane/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.46–1.59 (m, 1 H, 4-H), 2.14–2.25 (m, 1 H, 4-H), 2.86–2.98 (m, 1 H, 3-H), 2.99–3.10 (m, 2 H, 1-H, 5-H), 3.70 (s, 3 H, OCH_3), 4.02–4.18 (m, 2 H, OCH_2), 4.62–4.73 (m, 1 H, 2-H), 5.02–5.15 (m, 2 H, =CH), 5.76–5.88 (m, 1 H, =CH), 5.93 (d, *J* = 16.40 Hz, 1 H, =CH), 6.86 (d,

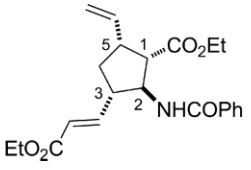
J = 9.6 Hz, 1 H, NH), 6.90–6.99 (m, 1 H, =CH), 7.39–7.45 (m, 2 H, Ar-H), 7.46–7.52 (m, 1 H, Ar-H), 7.70–7.76 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 36.8, 47.0, 49.3, 51.9, 52.2, 55.6, 61.5, 115.8, 122.5, 127.3, 129.0, 132.1, 139.6, 148.3, 166.9, 167.2, 174.5 ppm. MS (ESI): *m/z* = 372.28 $[M + H]^+$. $C_{21}H_{25}NO_5$ (371.43): calcd. C 67.91, H 6.78, N 3.77; found C 67.68, H 6.60, N 3.50.

Ethyl (1*S,2*S**,3*S**,5*R**)-2-Benzamido-3-[(*E*)-3-methoxy-3-oxoprop-1-en-1-yl]-5-vinylcyclopentanecarboxylate [(±)-16a]**



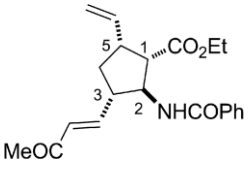
White solid (56 mg, 47 %). M.p. 115–118 °C. R_f = 0.58 (*n*-hexane/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.66–1.80 (m, 1 H, 4-H), 2.00–2.14 (m, 1 H, 4-H), 3.02–3.22 (m, 2 H, 3-H, 5-H), 3.24–3.35 (m, 1 H, 1-H), 3.69 (s, 3 H, OCH_3), 4.02–4.21 (m, 2 H, OCH_2), 4.38–4.48 (m, 1 H, 2-H), 4.98–5.12 (m, 2 H, =CH), 5.66–5.78 (m, 1 H, =CH), 5.90 (d, *J* = 15.6 Hz, 1 H, =CH), 6.70 (d, *J* = 7.6 Hz, 1 H, N-H), 6.94–7.03 (m, 1 H, =CH), 7.33–7.41 (m, 2 H, Ar-H), 7.42–7.49 (m, 1 H, Ar-H), 7.72 (d, *J* = 7.5 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 36.7, 44.8, 47.3, 51.9, 53.9, 59.6, 61.0, 116.8, 122.3, 127.3, 128.9, 132.0, 137.5, 149.4, 167.1, 168.0, 173.4 ppm. MS (ESI): *m/z* = 372.22 $[M + H]^+$. $C_{21}H_{25}NO_5$ (371.43): calcd. C 67.91, H 6.78, N 3.77; found C 67.70, H 6.64, N 3.54.

Ethyl (1*S,2*S**,3*S**,5*R**)-2-Benzamido-3-[(*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]-5-vinylcyclopentanecarboxylate (±)-16b**



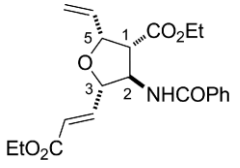
White solid (54 mg, 44 %). M.p. 145–147 °C. R_f = 0.68 (*n*-hexane/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16–1.39 (m, 6 H, CH_3), 1.69–1.83 (m, 1 H, 4-H), 2.01–2.17 (m, 1 H, 4-H), 3.05–3.25 (m, 2 H, 3-H, 5-H), 3.29–3.38 (m, 1 H, 1-H), 4.07–4.23 (m, 4 H, OCH_2), 4.32–4.41 (m, 1 H, 2-H), 4.99–5.14 (m, 2 H, =CH), 5.66–5.80 (m, 1 H, =CH), 5.90 (d, *J* = 14.8 Hz, 1 H, =CH), 6.26 (d, *J* = 7.6 Hz, 1 H, NH), 6.92–7.03 (m, 1 H, =CH), 7.37–7.45 (m, 2 H, Ar-H), 7.46–7.54 (m, 1 H, Ar-H), 7.67–7.76 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 14.7, 36.8, 44.9, 47.1, 53.7, 59.8, 60.8, 61.1, 116.8, 122.9, 127.4, 129.0, 132.0, 137.5, 148.9, 166.6, 167.9, 173.4 ppm. MS (ESI): *m/z* = 386.28 $[M + H]^+$. $C_{22}H_{27}NO_5$ (385.46): calcd. C 68.55, H 7.06, N 3.63; found C 68.38, H 6.84, N 3.34.

Ethyl (1*S,2*S**,3*S**,5*R**)-2-Benzamido-3-[(*E*)-3-oxobut-1-en-1-yl]-5-vinylcyclopentanecarboxylate [(±)-17]**



Brown oil (57 mg, 50 %). R_f = 0.44 (*n*-hexane/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.69–1.82 (m, 1 H, 4-H), 2.05–2.15 (m, 1 H, 4-H), 2.23 (s, 3 H, $COCH_3$), 2.95–3.07 (m, 1 H, 3-H), 3.11–3.30 (m, 2 H, 1-H, 5-H), 4.05–4.23 (m, 2 H, OCH_2), 4.47–4.59 (m, 1 H, 2-H), 4.99–5.14 (m, 2 H, =CH), 5.67–5.79 (m, 1 H, =CH), 6.1 (d, *J* = 16.8 Hz, 1 H, =CH), 6.62 (d, *J* = 7.2 Hz, 1 H, NH), 6.78–6.88 (m, 1 H, =CH), 7.35–7.43 (m, 2 H, Ar-H), 7.44–7.51 (m, 1 H, Ar-H), 7.72 (d, *J* = 7.5 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 27.3, 36.9, 44.9, 48.2, 54.1, 59.6, 61.1, 116.9, 127.4, 128.9, 132.0, 132.3, 137.4, 148.4, 168.0, 173.3, 199.1 ppm. MS (ESI): *m/z* = 356.36 $[M + H]^+$. $C_{21}H_{25}NO_4$ (355.43): calcd. C 70.96, H 7.09, N 3.94; found C 70.81, H 6.83, N 3.66.

Ethyl (2*R,3*R**,4*R**,5*S**)-4-Benzamido-5-[(*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]-2-vinyltetrahydrofuran-3-carboxylate [(±)-27]**



White solid (37 mg, 30 %). M.p. 156–162 °C. R_f = 0.40 (*n*-hexane/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13–1.37 (m, 6 H, CH_3), 3.63–3.74 (m, 1 H, 3-H), 4.06–4.27 (m, 4 H, OCH_2), 4.42–4.52 (m, 1 H, 4-H), 4.65–4.77 (m, 1 H, 5-H), 4.88–4.97 (m, 1 H, 2-H), 5.25 (d, *J* = 10.4 Hz, 1 H, =CH), 5.41 (d, *J* = 17.1 Hz, 1 H, =CH), 5.76–5.88 (m, 1 H, =CH), 6.09–6.18 (m, 1 H, =CH), 6.51 (d, *J* = 7.0 Hz, 1 H, NH), 7.06 (dd, *J* = 15.9, *J* = 5.5 Hz, 1 H, =CH), 7.38–7.46 (m, 2 H, Ar-H), 7.47–7.56 (m, 1 H, Ar-H), 7.71–7.80 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 54.0, 59.6, 61.0, 61.6, 80.4, 81.0, 118.9, 123.1, 127.4, 129.2, 132.4, 134.0, 144.5, 166.6, 168.1, 171.2 ppm. MS (ESI): *m/z* = 388.39 $[M + H]^+$. $C_{21}H_{25}NO_6$ (387.43): calcd. C 65.10, H 6.50, N 3.62; found C 64.88, H 6.27, N 3.39.

X-ray Structure Determination: A crystal of (±)-**16a** was immersed in cryo-oil, mounted in a MiTeGen loop, and measured at 100 K with a Rigaku Oxford Diffraction Supernova diffractometer using Mo-K_α (λ = 0.71073) radiation. The CrysAlisPro[12] program package was used for cell refinement and data reduction. Multiscan absorption correction (CrysAlisPro) was applied to the intensities before structure solution. The structure was solved by the charge-flipping method using the SUPERFLIP[13] software. Structural refinements were carried out using SHELXL-2014[14] with the SHELXLE[15] graphical user interface. Hydrogen atoms were positioned geometrically and constrained to ride on their parent atoms with C–H 0.95–0.99 Å, N–H 0.88 Å, and U_{iso} = 1.2–1.5·U_{eq} (parent atom). Crystallographic

Table 1. Crystal data.

	(±)-**16a**
Empirical formula	$C_{21}H_{25}NO_5$
Formula mass	371.42
T [K]	100(2)
λ [Å]	0.71073
Crystal system	monoclinic
Space group	$P2_1/c$
a [Å]	12.8600(4)
b [Å]	16.2546(4)
c [Å]	9.6694(3)
β [°]	97.616(3)
V [Å^3]	2003.40(10)
Z	4
$\varrho_{calcd.}$ [Mg/m^3]	1.231
$\mu(K_\alpha)$ [mm^{-1}]	0.088
No. of reflections	8937
Unique reflections	4938
GOOF (F^2)	1.031
R_{int}	0.0312
R_1[a] ($I \geq 2\sigma$)	0.0570
wR_2[b] ($I \geq 2\sigma$)	0.1370

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.

details are summarized in Table 1. CCDC 1524896 [for (±)-**16a**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Keywords: Metathesis · Chemoselectivity · Regioselectivity · Alkenes · Oxygen heterocycles · Hydrogen bonds

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